ART 34 AMDT

CLAIMS.

26. 07. 2004

We claim:

1. A process for manufacture of antihyperglycemic pharmaceutical composition as multi-layered tablet dosage form for once a day administration comprising: (75)

- preparation of type I granules for pH independent prolonged in-vitro release of biguanide or its pharmaceutically acceptable salts wherein, the type I granules comprise atleast 48% w/w of biguanide or its pharmaceutically acceptable salts of particle size less than 100 microns, blended with one or more polymers selected from alkylcellulose, hydroxyalkylcellulose, carboxyalkylcellulose, (meth)acrylic acid copolymers, xanthan gum, guar gum, alginates and their pharmaceutically acceptable salts, the polymer(s) being present in an amount of atleast 35% by weight of biguanide or its pharmaceutically acceptable salts;
- preparation of type II granules for immediate release of active pharmaceutical ingredient (API) or APIs or their pharmaceutical acceptable salts selected from thiazolidinediones and sulfonyl ureas wherein, the said API or APIs or their pharmaceutical acceptable salts is blended with atleast one excipient selected from fillers, disintegrants and binders;
- screening and sizing the prepared granules;
- treating the screened and sized granules with lubricants; and
- compressing the type I granules and type II granules to obtain layered tablets.

2. A process for the manufacture of composition as claimed in claim 1 wherein, layer-selective immediate release granules comprises of thiazolidinediones selected from Pioglitazone, Rosiglitazone, Troglitazone and their pharmaceutically acceptable salts preferably Pioglitazone HCl present in amount from 5% to 30% by weight of the corresponding layer.

3. A process as claimed in claim 1 wherein,

- atleast 48%w/w and preferably over 50%w/w of the prolonged release granules comprise of Metformin HCl of particle size less than 100 microns;
- Metformin HCl is blended with one or more polymers selected from alkylcellulose, hydroxyalkylcellulose, carboxyalkylcellulose, (meth)acrylic acid copolymers, xanthan gum, guar gum, alginates and their pharmaceutically acceptable salts, blending carried out in suitable mixer;
- Metformin HCl - polymer blend is wet granulated using a solvent optionally containing binders and plasticizers, in the presence of a granulation solvent being water or hydroalcoholic solution;

ART 34 AMDT

- the granulated mass is dried followed by sizing using comminuting mill or any other equipment suitable for the purpose, with appropriate mesh preferably around 1-mm mesh;
- the granules thus produced are mixed with talc, magnesium stearate and colloidal silicon dioxide.

4. A process as claimed in claim 1 and 2 wherein:

- the particle size of Pioglitazone HCl used is less than 30 microns;
- the Pioglitazone HCl is blended with fillers, disintegrants, binders, lubricants and permitted colours carried out in suitable mixer.

5. A process as claimed in claim 1, wherein the polymers used are preferably the mixture of alkylcellulose, hydroxyalkylcellulose, carboxyalkylcellulose, (meth)acrylic acid co-polymer, alginates or their pharmaceutically acceptable salts, xanthan gum and guar gum, preferably the mixture of one or more said celluloses with (meth)acrylic acid co-polymer or the mixture of one or more said celluloses with alginates or their pharmaceutically acceptable salts or the mixture of one or more said celluloses with alginates or their pharmaceutically acceptable salts and (meth)acrylic acid co-polymer or the mixture of one or more said celluloses with xanthan gum or the mixture of one or more said celluloses with guar gum.

6. A process as claimed in claim 5, wherein the alkylcellulose, hydroxyalkylcellulose and carboxyalkylcellulose is selected from methylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, methylhydroxyethylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose and calcium carboxymethylcellulose, the (meth)acrylic acid co-polymer is selected from esters of ethyl acrylate and methyl methacrylate, ethyl ammonium methacrylate and ethyl acrylate copolymers, ethylammonium methacrylate and methyl methacrylate copolymers, ethyl ammonium methacrylate and ethyl methacrylate copolymers, methacrylic acid and ethyl acrylate copolymers, methacrylic acid and methyl methacrylate copolymers , alginate and their acceptable sodium and calcium salt.

7. A process for the manufacture of the compositions as claimed in claim 6, wherein alkylcellulose, hydroxyalkylcellulose and carboxyalkylcellulose are selected from methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylhydroxyethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose,

carboxymethylcellulose, sodium carboxymethylcellulose and calcium carboxymethylcellulose present in an amount of atleast 35% by weight of the biguanide, more preferably 40-65 % by weight of the biguanide.

8. A process as claimed in claim 5 wherein the binary mixture of the polymers are selected from the mixture of hydroxypropylmethylcellulose and hydroxypropylcellulose; hydroxypropylmethylcellulose and hydroxyethylcellulose; hydroxypropylmethylcellulose and sodium carboxymethylcellulose; hydroxypropylmethylcellulose and sodium alginate; hydroxypropylmethylcellulose and Xanthan gum ; hydroxypropylmethylcellulose and guar gum; in the ratios ranging from 1 : 0.01 to 1 : 3.5.

9. A process as claimed in claim 5, wherein the mixture of three polymers is selected from hydroxypropylmethylcellulose, sodium carboxymethylcellulose and methacrylic acid copolymer and hydroxypropylmethylcellulose, sodium alginate and methacrylic acid copolymer used in ratios of 1 : 0.01: 0.1 to 1 : 3.5 : 0.5 respectively.

10. A process as claimed in claims 1, 3, 5 – 6, 8 – 9, wherein the one or more polymers used is atleast 35% by weight of the biguanide, most preferably 40 – 65 % by weight of the biguanide.

11. A process as claimed in claims 1, 3, 5 – 9 for the preparation of the pharmaceutical compositions in multi-layered / bi-layered tablet wherein the nominal viscosity at 20°C of a 2% w/w aqueous solution of hydroxypropylmethylcellulose used is not less than 3000cP, the nominal viscosity of a 1%w/w aqueous solution of sodium alginate at 20°C is not less than 50cP and the nominal viscosity of a 1%w/w aqueous dispersion of guar gum is not less than 2000 cP.

12. A process as claimed in claims 1, 3, 5 – 9 for the preparation of the pharmaceutical compositions in multi-layered / bi-layered tablet wherein, the nominal viscosity at 25°C of a 1% w/w aqueous solution of hydroxypropylcellulose is not less than 1500cP; hydroxyethylcellulose is not less than 1500cP; sodium carboxymethylcellulose is not less than 1500 cP and xanthan gum is not less than 1200 cP.

13. A process as claimed in claims 1 and 4 wherein the disintegrating agents are selected from the group comprising starch, sodium starch glycollate, crosscarmellose sodium, crosspovidone, pregelatinized starch, microcrystalline cellulose, hydroxypropylcellulose.

ART 34 AMDT

14. A process for the composition as claimed in claim 1, wherein the immediate release layer is a mixture of from 5% to 30% by weight of the thiazolidinediones and from 1 to 10% by weight of biguanides with excipients and other formulation ingredients.

15. A process according to claims 2 – 4, wherein Metformin HCl is in the range of 500mg -2000mg and Pioglitazone HCl equivalent to Pioglitazone is in the range of 15 - 60 mg.

16. A process for the manufacture of composition as claimed in claim 1, wherein the layers of the tablet are parallel to each other.

17. A process according to claim 1, wherein, the multilayer tablet is enrobed by soft gelatin ribbons for additional protection against oxidation, photodegradation, identification, ease of swallowing, taste masking and for aesthetic appeal without altering the dissolution profile.

18. An antihyperglycemic pharmaceutical composition as multi-layered tablet dosage form comprising atleast two layers wherein,

a) type I layer for pH independent prolonged in-vitro release of biguanide or its pharmaceutically acceptable salts comprises atleast 48% w/w of biguanide or its pharmaceutically acceptable salts of particle size less than 100 microns and atleast one polymer selected from alkylcellulose, hydroxyalkylcellulose, carboxyalkylcellulose, (meth)acrylic acid copolymers, xanthan gum, guar gum, alginates and their pharmaceutically acceptable salts, the polymer(s) being present in an amount of atleast 35% by weight of biguanide or its pharmaceutically acceptable salts; and

b) another layer for immediate release of active pharmaceutical ingredients (API) or APIs or their pharmaceutically acceptable salts selected from thiazolidinediones and sulfonyl ureas and atleast one excipient selected from fillers, disintegrants, binders and lubricants.

19. A pharmaceutical composition as claimed in claim 18, wherein the compressed layer containing biguanide and atleast one polymer selected from alkylcellulose, hydroxyalkylcellulose, carboxyalkylcellulose, (meth)acrylic acid copolymers, xanthan gum, guar gum, alginates and their pharmaceutically acceptable salts releases biguanide in the range of 25% – 45%, 50% – 80% and not less than 75% at the end of 1, 4, and 8 hours respectively.

20. A pharmaceutical composition as claimed in claim 18, wherein the compressed layer comprising API or APIs or their pharmaceutically acceptable salts releases not less than 80% of the said API or APIs or their pharmaceutically acceptable salts at the end of 30 minutes.

21. A pharmaceutical composition claimed in claims 18 – 20 wherein the prolonged release layer comprises of biguanide preferably Metformin HCl and the immediate release layer comprises of thiazolidinediones preferably Pioglitazone HCl with or without Metformin HCl.

22. A pharmaceutical composition as claimed in claim 21 wherein the immediate release layer comprises 5% to 30% by weight of thiazolidinediones and 1 to 10% by weight of Metformin HCl.

23. A pharmaceutical composition as claimed in claims 18 and 21 wherein, thiazolidinediones is selected from Pioglitazone, Rosiglitazone, Troglitazone and their pharmaceutically acceptable salts preferably Pioglitazone HCl and biguanides are selected from Metformin, Buformin and Phenformin and their pharmaceutically acceptable salts preferably Metformin HCl.

24. A pharmaceutical composition as claimed in claim 18, wherein the immediate release API or APIs or their pharmaceutically acceptable salts are present in an amount of from 5% - 30% by weight of the immediate release layer.

25. A pharmaceutical composition as claimed in claims 18 and 19, wherein the polymers used are preferably the mixture of alkylcellulose, hydroxyalkylcellulose, carboxyalkylcellulose, (meth)acrylic acid co-polymer, xanthan gum, alginates or their pharmaceutically acceptable salts, and guar gum, preferably the mixture of one or more said celluloses with (meth)acrylic acid co-polymer or the mixture of one or more said celluloses with alginates or their pharmaceutically acceptable salts or the mixture of one or more said celluloses with alginates or their pharmaceutically acceptable salts and (meth)acrylic acid co-polymer or the mixture of one or more said celluloses with xanthan gum or the mixture of one or more said celluloses with guar gum.

26. A pharmaceutical composition as claimed in claim 25, wherein the alkylcellulose, hydroxyalkylcellulose and carboxyalkylcellulose is selected from methylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, methylhydroxyethylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose and calcium carboxymethylcellulose, the (meth)acrylic acid co-polymer is selected from esters of ethyl acrylate and methyl methacrylate, ethyl

ART 34 AMDT

ammonium methacrylate and ethyl acrylate copolymers, ethylammonium methacrylate and methyl methacrylate copolymers, ethyl ammonium methacrylate and ethyl methacrylate copolymers, methacrylic acid and ethyl acrylate copolymers, methacrylic acid and methyl methacrylate copolymers , alginate and their acceptable sodium and calcium salt.

27. A pharmaceutical composition as claimed in claim 26, wherein alkylcellulose, hydroxyalkylcellulose and carboxyalkylcellulose are selected from methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylhydroxyethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose and calcium carboxymethylcellulose present in an amount of atleast 35% by weight of the biguanide, more preferably 40-65 % by weight of the biguanide.

28. A pharmaceutical composition as claimed in claims 25 – 27 wherein, the binary mixture of the polymers are selected from the mixture of hydroxypropylmethylcellulose and hydroxypropylcellulose; hydroxypropylmethylcellulose and hydroxyethylcellulose; hydroxypropylmethylcellulose and sodium alginate; hydroxypropylmethylcellulose and sodium carboxymethylcellulose; hydroxypropylmethylcellulose and Xanthan gum; hydroxypropylmethylcellulose and guar gum; in the ratios ranging from 1: 0.01 to 1: 3.5.

29. A pharmaceutical composition as claimed in claims 25 – 27 wherein, the mixture of three polymers is selected from hydroxypropylmethylcellulose, sodium carboxymethylcellulose and methacrylic acid copolymer and hydroxypropylmethylcellulose, sodium alginate and methacrylic acid copolymer used in ratios of 1 : 0.01: 0.1 to 1 : 3.5 : 0.5 respectively.

30. A pharmaceutical composition as claimed in claims 18 – 19, 25 – 29 wherein, the one or more polymers used is atleast 35% by weight of the biguanide, most preferably 40 – 65 % by weight of the biguanide.

31. A pharmaceutical dosage form comprising of type I granules as claimed in claims 1 and 18 wherein, the dosage form exhibits pH independent prolonged in-vitro release of biguanide or its pharmaceutically acceptable salts comprising atleast 48% w/w of biguanide or its pharmaceutically acceptable salts of particle size less than 100 microns and atleast one polymer selected from alkylcellulose, hydroxyalkylcellulose and carboxyalkylcellulose, (meth)acrylic acid copolymers, xanthan gum, guar gum, alginates and their pharmaceutically acceptable salts, the polymer(s) being present in an amount of atleast 35% by weight of biguanide preferably Metformin HCl.